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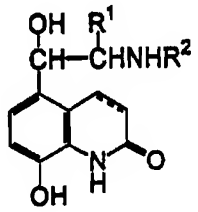
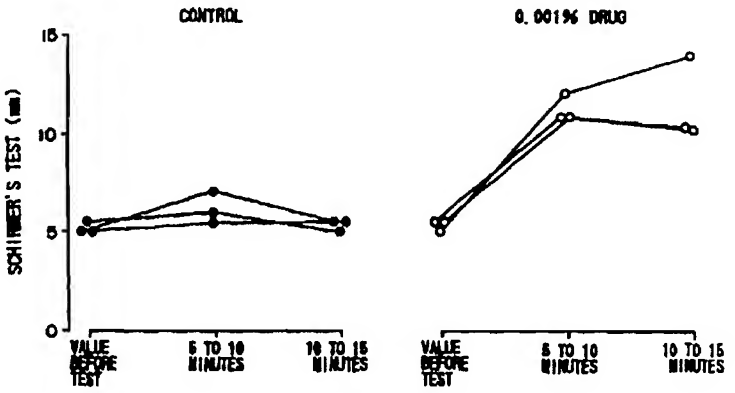
(54) Title: METHOD OF PREVENTING AND TREATING OPHTHALMIC INFLAMMATION AND/OR WOUND

(57) Abstract

A preventive and a remedy for ophthalmic inflammation and/or wound, which comprises at least one selected from carbostyril derivatives represented by formula (1), wherein R^1 and R^2 respectively indicate a lower alkyl group, and a bond between carbons of a carbostyril skeleton at the 3- and 4-positions indicates a single bond or a double bond, and salt thereof as an active ingredient.



(1)



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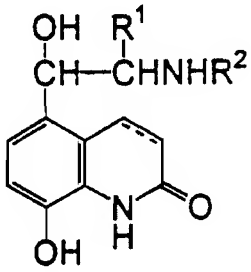
METHOD OF PREVENTING AND TREATING OPHTHALMIC INFLAMMATION AND/OR WOUND

<Technical Field>

This invention relates to a method of preventing and treating ophthalmic inflammation and/or wound.

<Background Art>

In Japanese Patent Publication No. 60-26784, there is disclosed that carbostyril derivatives represented by the formula (1):



(1)

[wherein R^1 and R^2 respectively indicate a lower alkyl group, and a bond between carbons of a carbostyril skeleton at the 3- and 4-positions indicates a single bond or a double bond] or salts thereof are effective as bronchodilators, peripheral vasodilators and antihypertensive drugs. Also, in U.S. Patent No. 4,322,425, there is disclosed that the above compounds are effective as remedies for glaucoma. Furthermore, in Japanese Laid-Open Patent Publication No. 64-52727, there is disclosed that the above compounds are useful as antiallergic eye drops.

However, ophthalmic inflammation and/or wound are caused by not only allergy, but also factors other than allergy. Thus, there have hitherto been required to develop

excellent remedies for ophthalmic inflammation and/or wound caused by factors other than allergy.

<Disclosure of the Invention>

The inventors have intensively studied about the carbostyril derivatives represented by the formula (1) or salts thereof. As a result, it has been found that the carbostyril derivatives or salts thereof, particularly 8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride accelerate the growth of various ophthalmic tissue cells such as ectocorneal cells, conjunctival cells, keratocytes, corneaendothelial cells, scleral fibroblasts, etc., and inhibit the destruction of the blood-aqueous humor shelf or the increase of the thickness of the cornea, whereby they are effective for various ophthalmic inflammations and/or wounds which are not related to allergy. Further, it has also been found that these compounds accelerate an increase in amount of lacrimal fluid and are extremely effective for hypolacrima alone or hypolacrima attended with various ophthalmic inflammations and/or wounds which are not related to allergy, keratoconjunctivitis sicca, xerosis of eye caused by insertion of contact lens, or Sjogren's syndrome. This invention has been accomplished based on the above knowledge.

That is, this invention provides a preventive and a remedy for ophthalmic inflammation and/or wound, which comprises carbostyril derivatives represented by the formula

(1) or salts thereof, particularly 8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride as an active ingredient.

The preventive and remedy for ophthalmic inflammation and/or wound of this invention can be suitably used for ophthalmic inflammations and/or wounds other than allergic ophthalmic diseases, for example, blepharitis, conjunctivitis, keratitis, scleritis, episcleritis, uveitis of anterior eye part, postoperative inflammation, chronic conjunctivitis, vernal conjunctivitis, lamellar keratitis, blepharitis marginalis, acute conjunctivitis, secretory epiphora, herpes corneae, prevention of corneal xerosis and protection of corneal disorder during an ophthalmic operation, intraocular irrigation (perfusion) and ablution upon ophthalmic operation (e.g. cataract, corpus vitreum, glaucoma, etc.), intraoperative miosis caused during cataract operation, postoperative inflammatory presentation, intraoperative/postoperative complication, hypolacrima, karatoconjunctivitis sicca, xerosis of eye due to insertion of contact lens, or Sjogren's syndrome.

<Brief Description of Drawings>

Fig. 1 is a graph illustrating the results of the pharmacological test 1.

Fig. 2 is a graph illustrating the results of the pharmacological test 2.

Fig. 3 is a graph illustrating the results of the pharmacological test 3.

Fig. 4 is a graph illustrating the results of the pharmacological test 4.

<Best Mode for Carrying Out the Invention>

In the above formula (1), the lower alkyl group represented by R^1 and R^2 include a straight- or branched-chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl and the like.

Among the compounds (1) to be used as the active ingredient in this invention, a compound containing an acid group can form a salt with a pharmacologically acceptable basic compound. Examples of the basic compound include metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, etc.; alkali metal carbonates or bicarbonates such as sodium carbonate, sodium bicarbonate, etc.; alkali metal alcoholates such as sodium methylate, potassium ethylate, etc. Further, among the compounds (1) to be used as the active ingredient in this invention, a compound having a basic group can form a salt easily with a pharmacologically acceptable acid. Examples of the acid include inorganic acids such as sulfuric acid, nitric acid, hydrochloric acid, hydrobromic acid, etc.; organic acids such as acetic acid, p-toluenesulfonic acid, ethanesulfonic

acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, benzoic acid, etc. In this invention, acid addition salts are particularly preferred.

Examples of the carbostyril derivative represented by the formula (1) include the followings.

8-Hydroxy-5-(1-hydroxy-2-isopropylaminobutyl) carbostyril

The preventive and remedy for ophthalmic inflammation and/or wound of this invention are prepared into a suitable dosage unit form by mixing the carbostyril derivative represented by the formula (1) or a salt thereof with a conventional carrier for ophthalmic preparation. As a dosage unit form, various normal forms can be optionally used. Examples of the form for local administration include ophthalmic ointment, eye drop, intraocular irrigating solution, etc., and examples of the form for general administration include tablet, granule, injection, etc. It is particularly preferred that the drug of this invention is prepared into the form of eye drop or intraocular irrigating solution.

The dose of the drug of this invention is not specifically limited, and it is advantageous that an amount of the active ingredient in the drug may be normally administered to an adult patient 2 to 3 times per day with a dairy dose of 0.01 to 0.5 mg, preferably 0.05 to 0.1 mg. Further, it is

preferred that an amount of the active ingredient in the drug is normally within a range of 0.04 to 2 % by weight.

The drug of this invention can be produced using a normal method. For example, it is produced by mixing the carbostyril derivative represented by the formula (1) or a salt thereof as the active ingredient with a suitable base, and adding excipients, if necessary. In case of ophthalmic ointment, eye drop, injection, etc., the drug of this invention is produced by subjecting to an additional sterilization treatment. The base to be used may be suitably selected according to the form of the drug. For example, when the ophthalmic ointment is produced, conventional emulsifiable bases, water-soluble bases, suspending bases, etc. can be used. Typical examples of the base include white vaseline, purified lanolin, liquid paraffin and the like. When the eye drop is produced, sterilized distilled water can be typically used as the base.

Further, solubilizers, stabilizers, buffering agents, antioxidants, antiseptics, etc. can also be blended in the drug of this invention. Examples of the solubilizer include polyoxyethylene glycol ethers such as sodium carboxymethyl cellulose, polyoxyethylene lauryl ether, polyoxyethylene oleyl ether, etc.; polyoxyethylene fatty acid esters such as polyethylene glycol monolaurate, polyethylene glycol higher fatty acid esters, polyoxyethylene sorbitan

monolaurate, polyoxyethylene sorbitan monooleate, etc. Examples of the stabilizer include hydroxypropylmethyl cellulose, polyvinyl alcohol, carboxymethyl cellulose, hydroxyethyl cellulose, glycerin, EDTA and the like. Examples of the buffering agent include sodium hydrogenphosphate, potassium hydrogenphosphate, boric acid, sodium borate, citric acid, sodium citrate, tartaric acid, sodium tartrate and the like. Examples of the antioxidant include sodium bisulfite, sodium thiosulfite, ascorbic acid and the like. Examples of the antiseptic include chlorobutanol, benzalkonium chloride, cetylpyridinium chloride, phenylmercury salt, thimerosal, phenethyl alcohol, methylparaben, propylparaben and the like.

When the drug of this invention has the form of the eye drop, it is preferred that the eye drop is isotonized with the lacrimal fluid. Therefore, it is preferred to add isotonicities such as sodium chloride, etc., if necessary. It is desirable to adjust the pH of the eye drop within a range of 5.5 to 8.5, preferably 6.5 to 7.5.

The drug of this invention thus obtained is administered using various administration methods according to the dosage unit form. In case of eye drop, it is dropped into eyes through a suitable eye dropper or sprayed to eyes through a spraying device. In case of ophthalmic ointment, it is applied into eyes. In case of tablet, granule, etc., it is orally administered. In case of injection, it is

subcutaneously, intramuscularly or intravenously administered. In any case, a desired effect can be obtained, similarly.

Furthermore, when applying this invention to an intraocular irrigating solution, it can be prepared using components which have normally been used in that technical field. It is preferred that the concentration of the carbostyril derivative represented by the formula (1) or a salt thereof in the intraocular irrigating solution is about 10^{-5} to 10^{-8} M, and the intraocular irrigating solution can be suitably used for ophthalmic operation, washing, etc. The irrigation may be normally conducted once a day.

<Examples>

Preparation Examples and Pharmacological Test Examples will be described hereinafter.

Preparation Example 1

8-Hydroxy-5-(1-hydroxy-2-isopropylaminobutyl) carbostyril hydrochloride	0.2 g
Benzalkonium chloride	0.01 g
Sodium dihydrogenphosphate	0.56 g
Potassium dihydrogenphosphate	0.8 g
Distilled water	suitable amount
Total	100 ml

The above ingredients were dissolved in distilled water, and then the resulting solution was sterilized and

filtered with a suitable filter paper to produce a drug in the form of eye drops of this invention.

Preparation Example 2

8-Hydroxy-5-(1-hydroxy-2-isopropylaminobutyl) carbostyril hydrochloride	0.1 g
Lactose	55 g
Corn starch	22 g
Crystal cellulose	22 g
Methyl cellulose	0.8 g

The above ingredients were mixed using a normal method, and then the resulting mixture was subjected to press molding to produce 1000 tablets.

Pharmacological Test 1

(lacrimal fluid increasing action test)

Nictitating membranes of New Zealand White domestic rabbits were excised and animals having no eye abnormality were selected. Tests were initiated after one week. An amount of lacrimal fluid was measured by using a modified primary process of Schirmer's test. That is, the domestic rabbit was fixed to a cylindrical fixing device and, after the animal calmed down, 50 μl of 0.4 % oxybuprocaine hydrochloride (0.4 % Benoxil, manufactured by Santen Seiyaku Co., Ltd.) was instilled into the right eye. After two minutes, 50 μl of a drug [8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride (Procaterol

hydrochloride) dissolved into a distilled water at a concentration of 0.001 % by weight] was also instilled into the right eye. Five minutes after instillation of the drug, a piece of Schirmer test paper was inserted into the inferior ophthalmic conjunctiva part. Five minutes later, the Schirmer test paper was removed to measure the length of the part of the paper wet with tear (for five minutes between 5 and 10 minutes after instillation of the drug). Furthermore, a Schirmer test paper was again inserted into the inferior ophthalmic conjunctiva part to measure the amount of lacrimal fluid from 10 to 15 minutes after instillation of the drug.

The results are shown in Fig. 1.

Pharmacological Test 2

(growth acceleration activity test to various cells)

(1) Sampling of tissue

New Zealand White domestic rabbits were slaughtered by intravenously administering 250 mg of pentobarbital and their eyeballs were excised. After the tunica conjunctiva bulbi was removed, the cornea and sclera were separated using ophthalmic scissors. The cornea was placed in phosphate buffered saline (PBS) and the Descemet's membrane was removed using tweezers under stereoscopic microscopy. The cornea sampled from the eyeball was sufficiently washed with PBS and the cells were cultured by the following method to measure the growth acceleration activity of the drug [8-hydroxy-5-(1-

hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride (Procaterol hydrochloride)] on the respective cells.

(2) Ectocorneal cells

A piece 2 to 3 mm square of the cornea was made from the cornea using a razor. The piece of the cornea was closely placed on a dish for tissue culture and, after a Dulbecco modified Eagle's medium F12 (DME/F-12, 1:1) containing 10 % fetal calf serum (FCS), 10 ng/ml of an epidermal growth factor (EGF) and 10 μg/ml of insulin was added, it was cultured at 37 ℃ in 5 % CO_2 for two days. After the piece of the cornea was removed, the culturing was conducted for three additional days. The removed piece of the cornea was used for culturing keratocytes.

(3) Keratocytes

A piece of the cornea was closely placed on a dish for tissue culture and, after a Dulbecco modified Eagle's medium (DMEM) containing 10 % FCS was added, it was cultured at 37 ℃ in 5 % CO_2 to obtain growth-out keratocytes from the piece of the cornea.

(4) Measurement of growth acceleration activity

The respective cultured cells were subjected to a 0.25 % trypsin-0.01 % EDTA treatment to disengage the cells from the surface of the dish. The disengaged cells were suspended in the medium used for culturing the respective cells and, after centrifuging at 1000 rpm for five minutes,

the medium was removed under vacuum. The cell pellets were again suspended in the medium, and the cell density was adjusted to 4 x 10^4 cells/ml. The cells (0.51 ml/well) were then inoculated in a cell culture plate with 24 holes and cultured overnight at 37 ℃ in 5 % CO_2. After exchanging with fresh medium, 5 μl/well (n=3) of a dilution series (2 x 10^{-5}M, 2 x 10^{-4}M, 2 x 10^{-3}M and 2 x 10^{-2}M) of an aqueous solution of a drug [8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride] was added and the cells were cultured for two to three days. Then, 30 μl/well of a 0.2 % solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added and, after culturing for four hours, 150 μl of a 20 % SDS (sodium dodecyl sulfate) solution was added to dissolve the cells. The absorbance (570 nm, control: 690 nm) of the cell-dissolved solution was measured. Furthermore, a solution obtained according to the same manner as that already described except that no drug was added was used as the control. The potency of the drug was calculated according to the following formula:

$$\frac{\text{Drug Absorbance in 570 nm} - \text{Drug Absorbance in 690 nm}}{\text{Control Absorbance in 570 nm} - \text{Control Absorbance in 690 nm}} \times 100\ (\%)$$

The results are shown in Fig. 2.

Pharmacological Test 3

(action of the carbostyril derivative of formula (1) on blood-aqueous humor shelf after ophthalmic operation of rabbit)

Rabbits (New Zealand White derivation, weight of 2 to 3 kg) were preliminary bred for about one week and anesthetized by intravenously administering pentobarbital. Then, a carbostyril derivative [i.e., 8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride (Procaterol hydrochloride)] was dissolved in physiological saline at a different concentration of 10^{-8} M, 10^{-7} M, 10^{-6} M and 10^{-5} M and the irrigating solution thus obtained was subjected to irrigation of the anterior chamber to measure the amount of protein in an eluate from the anterior chamber using a Blo Rad protein assay.

The results are shown in Fig. 3. As apparent from Fig. 3, the destruction of the blood-aqueous humor shelf after operation was inhibited in dependence on the dose by adding the carbostyril derivative to an intraocular irrigating solution.

Pharmacological Test 4

(action of the carbostyril derivative of formula (1) on edema of corneosclera fragment extracted from rabbit)

Rabbits (New Zealand White derivation, weight of 2 to 3 kg) were preliminary bred for about one week and slaughtered by intravenously administering pentobarbital. Then, eyeballs were extracted to prepare a corneosclera

fragment. A carbostyril derivative [i.e., 8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride (Procaterol hydrochloride)] was dissolved in physiological saline at a concentration of 10^{-6} M and the irrigating solution thus obtained was subjected to irrigation of the corneal endothelium side to measure the thickness of the cornea using an Ultrasonic Pachymeter.

The results are shown in Fig. 4. In Fig. 4, "△ Thickness" means the increased thickness of the cornea. As apparent from Fig. 4, the corneal transition of the aqueous humor attended with disorder endothelialis cornea was prevented by adding the carbostyril derivative to an intraocular irrigating solution, which results in inhibition of the increase of the thickness of the cornea attended with corneal edema.

CLAIMS

1. A method of preventing or treating ophthalmic inflammation and/or wound, which comprises locally or generally administering a drug containing at least one selected from carbostyril derivatives represented by the formula:

wherein R^1 and R^2 respectively indicate a lower alkyl group, and a bond between carbons of a carbostyril skeleton at the 3- and 4-positions indicates a single bond or a double bond, and salts thereof as an active ingredient, provided that the preventive and remedy for ophthalmic inflammation due to allergy are excluded.

2. A method of increasing lacrimal fluid, which comprises locally or generally administering a drug containing at least one selected from carbostyril derivatives and salts thereof defined in claim 1 as an active ingredient.

3. A method of intraocular irrigation and ablution upon ophthalmic operation, which comprises locally or

generally administering a drug containing at least one selected from carbostyril derivatives and salts thereof defined in claim 1 as an active ingredient.

4. A method of accelerating the growth of ophthalmic tissue cells such as ectocorneal cells, conjunctival cells, keratocytes and scleral fibroblasts, which comprises locally or generally administering a drug containing at least one selected from carbostyril derivatives and salts thereof defined in claim 1 as the active ingredient.

5. A method of preventive or treating blepharitis, conjunctivitis, keratitis, scleritis, episcleritis, uveitis of anterior eye part, postoperative inflammation, chronic conjunctivitis, vernal conjunctivitis, lamellar keratitis, blepharitis marginalis, acute conjunctivitis, secretory epiphora, herpes corneae, corneal xerosis and corneal disorder during an ophthalmic operation, intraoperative miosis caused during a cataract operation, postoperative inflammatory presentation, intraoperative/postoperative complication, hypolacrima, karatoconjunctivitis sicca, xerosis of eye due to insertion of contact lens, or Sjogren's syndrome, which comprises locally or generally administering a drug containing at least one selected from carbostyril derivatives and salts thereof defined in claim 1 as an active ingredient, provided that ophthalmic inflammation due to allergy is excluded.

6. A method of inhibiting the destruction of a blood-aqueous shelf, which comprises locally or generally administering a drug containing at least one selected from the carbostyril derivatives defined in claim 1 and salts thereof as an active ingredient.

7. A method of inhibiting the increase of the thickness of cornea, which comprises locally or generally administering a drug containing at least one selected from the carbostyril derivatives defined in claim 1 and salts thereof as an active ingredient.

8. A method according to any one of claims 1 to 7, wherein the active ingredient is 8-hydroxy-5-(1-hydroxy-2-isopropylaminobutyl)carbostyril hydrochloride.

9. A preventive and a remedy for ophthalmic inflammation and/or wound, which contains at least one selected from carbostyril derivatives represented by the formula:

wherein R^1 and R^2 respectively indicate a lower alkyl group,

and a bond between carbons of a carbostyril skeleton at the 3- and 4-positions indicates a single bond or a double bond, and salts thereof as an active ingredient, provided that the preventive and remedy for ophthalmic inflammation due to allergy are excluded.

FIG. 1

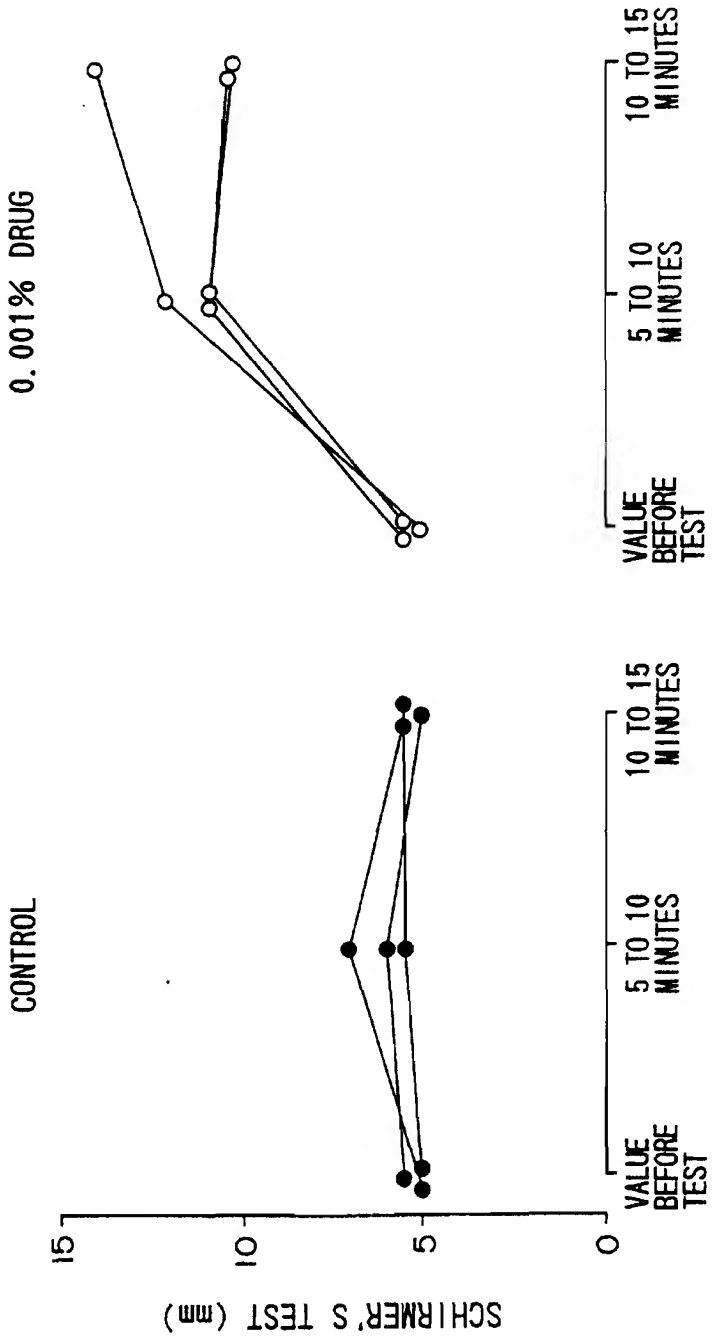
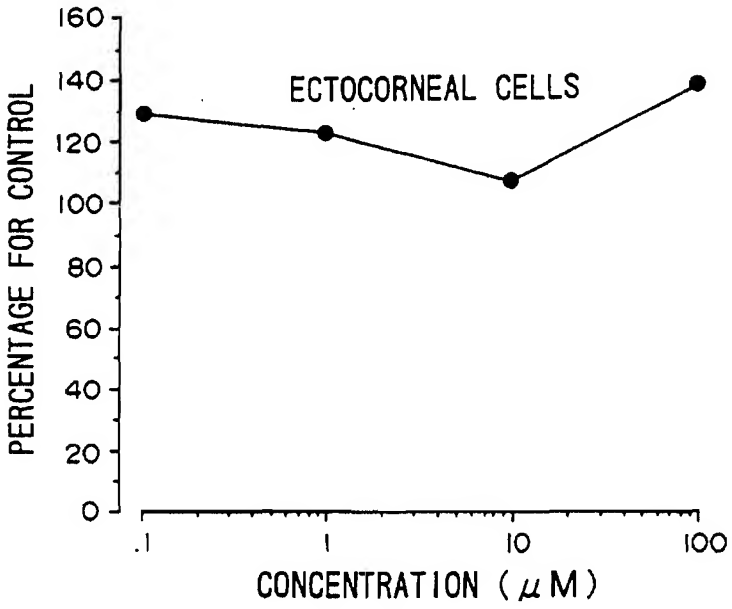

SCHIRMER'S TEST (mm)
15
10
5
0
CONTROL
0.001% DRUG
VALUE BEFORE TEST
5 TO 10 MINUTES
10 TO 15 MINUTES

FIG. 2A


ECTOCORNEAL CELLS
PERCENTAGE FOR CONTROL
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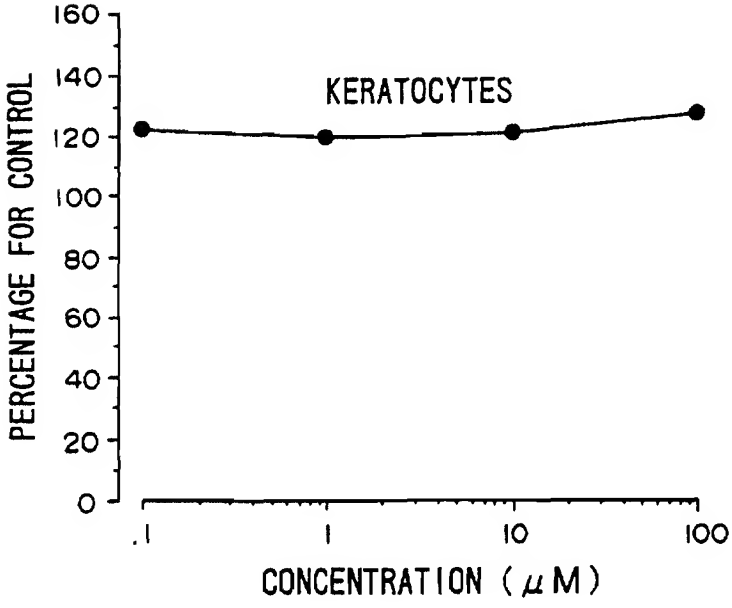
120
100
80
60
40
20
0
.1
1
10
100
CONCENTRATION (μM)

FIG. 2B


KERATOCYTES
PERCENTAGE FOR CONTROL
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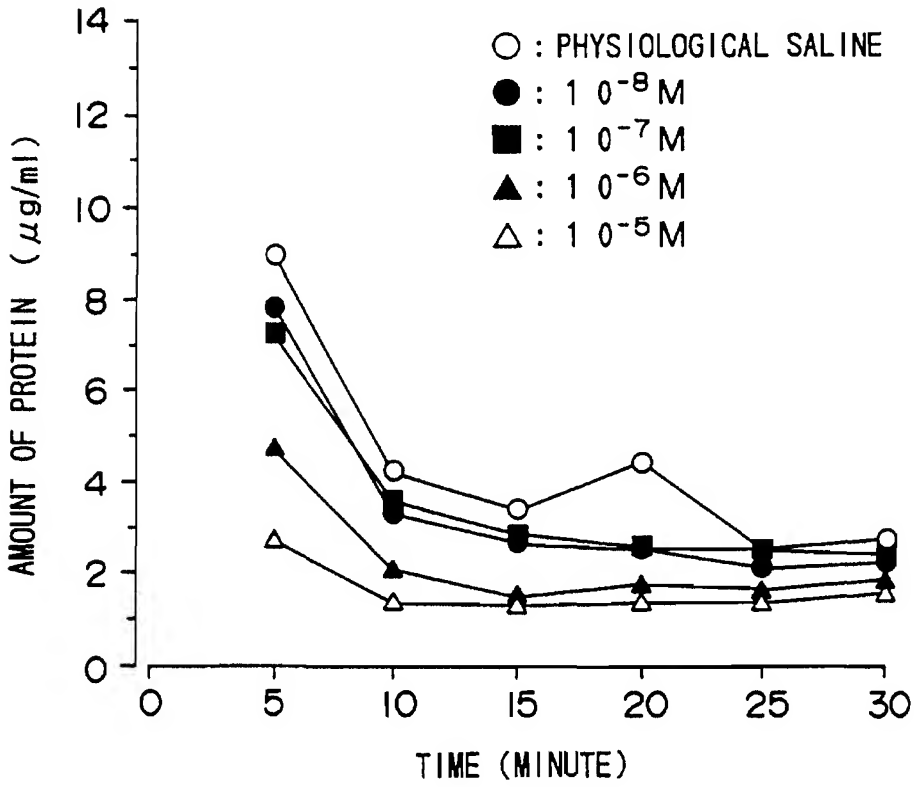
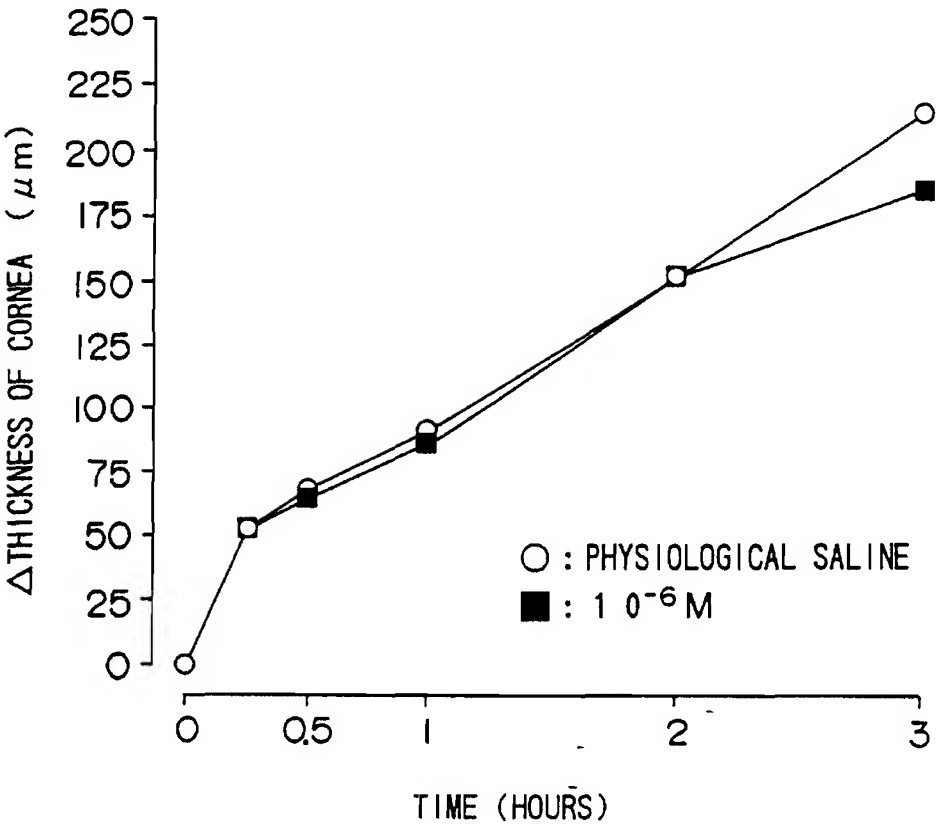
120
100
80
60
40
20
0
.1
1
10
100
CONCENTRATION (μM)

FIG. 3



CONDITIONS OF IRRIGATION : 1.5 ml/MINUTE FOR 30 MINUTES

FIG. 4


250
225
200
175
150
125
100
75
50
25
0
ΔTHICKNESS OF CORNEA (μm)
○ : PHYSIOLOGICAL SALINE
■ : 10⁻⁶M
0
0.5
1
2
3
TIME (HOURS)

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/JP 95/01570

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JPN.J.CLIN.OPHTHALMOL., vol.46, no.10, October 1992 pages 1437 - 1440 Y.SAKUMA ET AL. 'Suppression of ocular reactions in cedar pollinosis by procaterol hydrochloride eyedrops' see abstract ---	9
X	YAKURI TO CHIRYO, vol.21, no.9, September 1993 pages 3075 - 3084 Y.YAMAMOTO ET AL. 'Usefulness of Procaterol Eyedrops on Experimental Models of Allergic Conjunctivitis' see abstract --- -/--	9

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 November 1995	17.11.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Theuns, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/JP 95/01570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 89-104873 & JP,A,01 052 727 (SANTEN SEIYAKU KK) 28 February 1989 see abstract ---	9
X	EP,A,0 020 765 (OTSUKA PHARMACEUTICAL CO., LTD.) 7 January 1981 see the whole document ---	9
X	DATABASE FILE 399: CA SEARCH host: dialog an=123000465 see abstract & ATARASHII GANKA, vol.12, no.3, 1995 pages 466 - 468 Y.SAKUMA -----	9

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 95/01570

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-8 are directed to a method of treatment of the human/animal body, the search has been based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 95/01570

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0020765	07-01-81	JP-C- 1338708	29-09-86
		JP-A- 55013241	30-01-80
		JP-B- 61001007	13-01-86
		CH-A- 643143	30-05-84
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		WO-A- 8000215	21-02-80
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		SE-A- 8001981	13-03-80